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The Glymphatic System and New Etiopathogenic Hypotheses Concerning Glaucoma Based on Pilot Study on Glaucoma Patients Who Underwent Osteopathic Manipulative Treatment (OMT)

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Abstract. Purpose Malfunction of the lymphatic or glymphatic system recently shown in the brain, seems to play an important role in central neurodegenerative pathologies through a build-up of neurotoxins. Recent studies have shown functional links between aqueous humour and cerebrospinal fluid via the glymphatic system, offering new perspectives and unifying theories on the vascular, biomechanical and biochemical causes of chronic and open-angle glaucoma (POAG). The aim of this randomized pilot study is to compare the variations in intraocular pressure between 20 cases of compensated POAG under pharmacological therapy and 20 glaucoma patients undergoing osteopathic treatment, hypothesizing that this manipulation can influence intraocular pressure. Materials and Methods The 40 patients under study, all covered by the Helsinki convention, were randomly divided into 2 groups (treated group or TG and control group or CG). The 40 patients were chosen from compensated glaucoma sufferers, who required neither changes in therapy nor operations which would affect their eye pressure which was measured both before and after manipulative osteopathic treatment scheduled into 4 sessions at intervals of 7.3 and 150 days, then compared with the control group (20 patients) who were undergoing pharmacological treatment only. Results The average IOP in the TG was compared with the CG throughout the entire treatment cycle showing a statistically inconclusive reduction in the right eye RE P-value (0.0561), while for the left eye a significant effect was shown LE (0.0073). The difference between the reduction in IOP between TG and CG was observable 10 months after the first session or rather 5 months after the last, and demonstrable during a check-up 13 months after the beginning of the study, or rather 8 months in absence of treatment with a highly significant statistical p-value (0.000434). Conclusions This study has shown that manipulative osteopathic treatment can affect intraocular pressure after each session and that the pressure is significantly lower even months after the last treatment session.

Keywords: Glaucoma, Glymphatic System, Osteopathic Manipulative Treatment (OMT).

Introduction and Aims

The causes of primary open angle glaucoma are today still unclear. The recent discovery of a lymphatic system in the brain and the eye [1–5], called the glymphatic system, appears to shed new light on the etiopathogenic causes of this disease, bringing together various different hypotheses: vascular, biomechanical and biochemical [6].

Intraocular pressure (IOP) is the principal risk factor for glaucoma and the main factor which can be rectified by therapy [7]. The vascular dysregulation of which Flammer speaks [8, 9], is in reality a rectifiable factor, but one which is difficult to identify on the spot.

In certain cases of normal tension glaucoma (NTG), damage to the visual field occurs while in cases of high ocular pressure, damage to the visual field may be absent [10]. In patients with NTG, the pressure of the cerebrospinal fluid (CSF) which is equivalent to the intracranial pressure, appears to be lower [10–13], while according to other studies, in patients with high intraocular pressure who present no functional damage the CSF pressure is higher [14, 15]. Other studies substantiate the preceding hypotheses explaining how the influence of translaminar pressure has a determining role in open-angle glaucoma [16–18].

Conversely, a retrospective study of CSF pressure in NTG puts the preceding hypotheses in doubt, suggesting changes in the investigative methodology, with the aim of proving the validity of the new theories concerning translaminar pressure [19].

The fact that bloodflow can also be lower in other parts of the body, and that the reduction in the flow of blood to the eye is often a precursor to glaucomatous damage, presupposes – as has also been shown by recent systematic revisions – that haemodynamic changes can be at least in part a primary factor in patients affected by glaucoma [8, 9]. This hypothesis would explain the value of manipulative osteopathic treatment (OMth), including in other areas, not only the cervical-cranial area, aimed at an overall improvement in lymphatic drainage and vascular perfusion inside the cranium [20–26].

In the osteopathy literature we can find a range of studies which propose techniques for the eyes and the orbital areas and which demonstrate the influence of OMth on IOP [27–35].

The aim of this work is to identify the effects and their duration of a series of osteopathic treatments on ocular pressure, on a sample of patients affected by open-angle glaucoma (POAG), who were stable and under medication.

Materials and Methods

40 patients, all of Caucasian extraction, for a total of 80 eyes, were monitored for 13 months. As glaucomatous disease often strikes where the damage and the progression do not manifest themselves symmetrically, we chose to evaluate the effect of the OMth on both eyes, to establish whether there were different effects of the OMth in either of the eyes.

The overall average age of the 40 patients was 71.2 years (from 34 to 83 years) all with diagnosis of stable and medicated POAG. Patients who were recorded with increased eye pressure or reductions in the visual field or visual acuity to the extent where the topical treatment would have to be temporarily modified or who would require an anti-glaucoma operation or the extraction of a cataract, were eliminated from the case study.

The treated group (TG) had an average age of 70.5 ± (from 34 to 87 years), that of the patients of the control group (CG) 71.8 ± (from 51 to 95 years).

In the treated patients, the average defect (AD) in the right eye (RE) was −5.55 dB, in the left eye (LE) −7.06 dB; in the controls the RE had an AD equivalent to −6.51 dB and the LE equivalent to −4.65 dB.

The patients were randomized into two groups, TG and CG (20 per group) with Excel 2010, in line with the inclusion and exclusion criteria Table 1.

Every patient had a preceding follow-up of a minimum of three years and maximum of ten, with at least 3 visual field tests, at least 1 for each year. 4 osteopathic treatments were performed at regular intervals for all patients, from 1 week to 5 months, according to Table 2. The CG was checked at the same intervals as for the measurement of ocular pressure.

Informed consent was obtained from every patient in the study, as set out in the Helsinki declaration. Every member of the TG provided a detailed personal medical history and underwent a general health-check to exclude local or general pathologies which could falsify or compromise the OMth (following the inclusion and exclusion criteria). From the second examination onwards, they completed a quality survey questionnaire in order to suspend the OMth in case of the appearance of eventual side effects due to the treatment Table 3 [36].

In the TG, the ocular pressure was measured immediately before and immediately after the OMth, to detect any variation. Ocular pressure was measured for all 40 patients in a seated position, using a Goldmann pressure apparatus. Ocular pressure was measured in the CG (one single

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
Clinical diagnosis of bilateral open-angle glaucoma (40 patients) POAG, divided into two randomized groups.
Follow-up of at least 3 years before the start of the study
Reliable visual field tests (at least 3), one per year
Last visual field test before the experiment not previous to 3 months from the beginning of the study
Glaucoma under pharmacological control
Pachimetry readings fall in the normal range
Patients are cooperative
Signing of the informed consent form
Exclusion Criteria
Other types of Glaucoma
Any kind of ocular or systemic anomaly or pathology which would render the osteopathic manipulation unreliable, impracticable, or impossible to evaluate
Change in pressure reduction therapy during the course of the study
Anti-glaucoma operations or cataract operations during the course of the study
Contraindications to the OMth
Patients with low compliance

Table 2. Methods and timescales for the osteopathic treatment and tonometry testing.

– Complete medical history of the patient
– Treatment to increase neuro-lymphatic drainage and reduce neurotoxicity: favouring the drainage of the cervical lymphatic ducts by means of manipulation of the cranial and periorbital sutures, and visceral manipulation. Average duration is 50 minutes.
– Timescale for the osteopathic treatments: 1st treatment TIME ZERO, 2nd treatment after a week, 3rd treatment after a month, 4th and last treatment after 5 months from the first
– Tonometry before and after every osteopathic treatment and at 10 and 13 months from the beginning of the study.
– Survey of the appreciation of the treatment.

Table 3. Questionnaire on the appreciation of the treatment.

• Have you noticed any changes in the pain or discomfort you were experiencing?
• Have you noticed any new pains emerge since your last treatment?
• Have you noticed any changes in your daily/work activities?
• Have you noticed any changes in your sporting activity?
• Have you noticed any changes in your digestion?
• Have you noticed any changes in your bowel movements?
• Have you noticed any changes in your sleep patterns?
• Drowsiness? Waking up during the night? Hours of sleep? Morning waking times?
• Have you experienced episodes of emotional stress, anxiety, or feeling unwell lately?
• Have you injured yourself recently?

measurement) with no osteopathic treatment, at the same intervals as the treated patients.

The visual field test was carried out on each of the 40 patients with a Humphrey apparatus, programme 30/2, threshold test, not previous to three months from the beginning of the study and not later than three months from the end.

The OMth wasn't directed exclusively at the cranial-cervical area; rather it had the aim of favouring the systemic and local circulation and of acting on the somatic dysfunction (SD). SD is defined as an expression of a compromised or altered function of somatic structures or – in other words – skeletal, arthrodial and myofascial structures, and their related vascular, lymphatic and neural components. SD is considered to be one of the principal reversible and functional factors which influence homeostasis, and can be the cause of many pathologies even in areas well away from where the dysfunction is actually located, and whose normalization is considered essential to restore normal mobility and functioning of the entire somatic system (body).

SD is identified through palpation of various structures where the compromised functionality of the tissues has its origin. Connective tissue alterations bring about an individual reaction manifested in changes in the texture of the tissue (T); structural asymmetry (A); restricted motion (R); and tenderness (T); these palpation parameters which are used to identify SD, are known by the acronym T.A.R.T. [37].

The osteopathic aspect was broken down into four phases:

- Recording of patients' medical history;
- Osteopathic examination;
- OMth;
- Exit test;

Patients' Medical History

Patients are invited to sit at a desk where their personal medical history is recorded. Further to this initial questionnaire, a carefully catalogued record is made of any eventual pain, previous conditions, surgical operations undergone, serious accidents suffered, current medication regimes and any irregular bodily function parameters regarding fatigue, sleep patterns, digestion, bowel movement and urination [38].

Osteopathic Examination

Everyone in the TG underwent the following osteopathic examination for the initial evaluation (entry test) and after the OMth (exit test).

- DIAPHRAGM MOBILITY TEST

  All the patients underwent the diaphragm breathing test in order to determine whether there were any breathing imbalances in the diaphragm movement, or any mechanical restrictions which could influence the correct exchange of the fluids (blood and lymph) [39, 40] or the circulation of the CSF [41]. The tests were carried out by palpation and manual examination of the following musculoskeletal structures: rib margins, costo-xifoid angle, sternum, ribs, clavicles. Manual examination of thoracic expansion was also performed in order to determine the range of diaphragm breathing movement [38].
- SPINAL COLUMN and RIBCAGE MOBILITY TEST

  These tests are carried out with the patient seated and prone and are used to identify SD. Any eventual SD detected in the spinal column or the ribcage, were identified by mobilization and palpation of the vertebral segments [38].
- ABDOMINAL PALPATION

  The next phase is abdominal palpation, whose purpose is to identify any eventual correspondence

between the autonomous nervous system, a dysfunctional vertebral tract known as a "facilitated segment" and the viscera which are innervated from this region. A facilitated segment is diagnosed on the T.A.R.T. model and by vertebral mobilization which shows a regular and rhythmic lateral inclination of the vertebral transverse processes, on the side of the body where the organ is located [38, 42, 43].

- CRANIO-SACRAL TEST

  These tests are carried out with the patient in the supine position and are aimed at evaluating the craniosacral system and any eventual alterations in the expression of this movement. The approach to the cranium was analogous to the evaluation of the other areas of the body, testing the mobility and the asymmetries of the cranial bones and of the sacral bone.

By means of palpation the tension vector is identified and traced to its origin, distinguishing the following layers: skin, fascial tissue, bone, pachymeninges (dura mater).

In one of these layers the origin of the tension vector can be found, at which point the evaluation of the somatic dysfunction through the mobility of the revealed structure can proceed [38, 42].

Once the SD had been understood on three levels: musculoskeletal, visceral or cranio-sacral the OMth began. The treatment carried out at every session didn't represent a series of previously chosen techniques, but was based exclusively on the clinical evidence gathered in the initial tests by means of osteopathic palpation. This practice is known as "blackbox" [44]. At the end of the treatment Exit Tests were performed (equivalent to the entry tests), in particular in the area any eventual SD was discovered. On average the osteopathic manipulation lasted for 50 minutes and was carried out with patients either lying on their sides, or in supine or prone positions.

Results and Statistical Analysis

The appreciation survey questionnaire and the recording of the side effects, particularly in respect of the OMT, revealed a unanimously favourable reaction in the treated patients. None of the patients reported side effects or negative reactions from the manipulation throughout the entire period of the treatment, nor for months afterwards.

The following statistical tests were applied:

The May-Witney test, which involves a comparison between the group of treated and non-treated patients

The Wilcoxon test, which involves the comparison in a longitudinal sense

A comparison test from a group of three individual treatments, before the osteopathic manipulation, at a distance of 5 months and a distance of 13 months.

The average of the ocular pressure in the TG was compared with the CG throughout the treatment cycle showed a statistically significant lowering in both eyes (RE $p < 0.0561$, LE $p < 0.0073$). The reduction of the ocular pressure in the TG compared to the CG was maintained at 10 months from the first treatment or rather after 5 months from the last and was shown to be present even at check-up after 13 months from the beginning of the study or rather 8 months in absence of treatment ($p < 0.000434$).

	TIME 0		TIME 1 WEEK		TIME 1 MONTH		TIME 5 MONTHS		10 MONTHS	13 MONTHS
RE	1_0	1_1	2_0	2_1	3_0	3_1	4_0	4_1	5_0	6_0
tratt1	17	15	18	17	18	16	17	16	16	18
tratt2	13	10	12	10	15	13	13	10	12	10
tratt3	19	16	13	13	16	15	15	14	12	10
tratt4	17	16	16	14	15	13	17	16	16	16
tratt5	16	15	15	14	15	14	12	12	12	11
tratt6	20	18	18	18	15	15	15	10	17	15
tratt7	21	15	21	16	16	16	24	23	21	19
tratt8	18	16	17	16	18	17	16	16	16	17
tratt9	15	12	16	13	14	10	16	11	12	14
tratt10	15	10	17	15	20	16	16	15	16	16
tratt11	16	12	15	12	14	12	12	12	14	14
tratt12	18	17	17	16	14	13	18	14	15	14
tratt13	17	15	15	15	15	13	13	14	16	14
tratt14	16	14	19	17	18	17	17	15	15	15
tratt15	20	18	19	17	18	18	19	18	19	16
tratt16	12	12	14	12	15	13	14	10	12	11
tratt17	15	13	15	14	15	15	15	14	16	17
tratt18	15	13	16	14	16	18	14	13	13	27
tratt19	18	12	17	12	19	18	20	15	18	14
tratt20	17	14	16	14	16	15	16	14	15	17

RE: Right eye; OMT: Osteopathic manipulative treatment.

TZERO IOP BEFORE OMT	1_O	TZERO IOP AFTER OMT	1_1
T7 DAYS IOP BEFORE OMT	2_O	T7 DAYS IOP AFTER OMT	2_1
T1 MONTH IOP BEFORE OMT	3_O	T1 MONTH IOP AFTER OMT	3_1
T5 MONTHS IOP BEFORE OMT	4_O	T5 MONTHS IOP AFTER OMT	4_1
T10 MONTHS IOP BEFORE OMT	5_O	T13 MONTHS IOP BEFORE OMT	6_O

	TIME 0		TIME 1 WEEK		TIME 1 MONTH		TIME 5 MONTHS		10 MONTHS	13 MONTHS
LE	1_0	1_1	2_0	2_1	3_0	3_1	4_0	4_1	5_0	6_0
tratt1	17	15	16	16	16	15	16	16	15	16
tratt2	18	17	18	17	16	16	15	14	16	13
tratt3	18	17	13	12	17	15	15	12	12	10
tratt4	17	16	16	14	15	13	15	14	15	14
tratt5	17	15	14	13	15	13	14	14	12	12
tratt6	20	18	20	20	15	15	15	11	17	16
tratt7	17	15	18	18	16	16	22	20	21	20
tratt8	18	17	17	17	18	16	16	16	17	18
tratt9	16	10	15	13	13	11	15	10	12	13
tratt10	17	15	16	15	20	18	16	15	15	16
tratt11	15	15	16	12	15	12	12	13	13	18
tratt12	19	16	17	16	17	16	17	13	15	14
tratt13	18	16	16	14	15	13	13	14	15	13
tratt14	20	15	18	17	20	18	18	16	16	16
tratt15	19	18	18	17	20	18	18	17	19	19
tratt16	12	12	15	12	14	11	15	12	12	12
tratt17	15	12	16	14	15	14	16	14	17	17
tratt18	16	13	16	13	18	15	14	10	13	20
tratt19	16	12	18	13	18	18	19	16	18	14
tratt20	17	15	16	15	19	18	16	15	17	18

LE: Left eye; OMT: Osteopathic manipulative treatment.

TZERO IOP BEFORE OMT	1_O	TZERO IOP AFTER OMT	1_1
T7 DAYS IOP BEFORE OMT	2_O	T7 DAYS IOP AFTER OMT	2_1
T1 MONTH IOP BEFORE OMT	3_O	T1 MONTH IOP AFTER OMT	3_1
T5 MONTHS IOP BEFORE OMT	4_O	T5 MONTHS IOP AFTER OMT	4_1
T10 MONTHS IOP BEFORE OMT	5_O	T13 MONTHS IOP BEFORE OMT	6_O

RE	1_0	2_0	3_0	4_0	5_0	6_0
ctrl1	18	18	17	20	18	21
ctrl2	17	17	17	19	18	18
ctrl3	16	18	18	18	19	20
ctrl4	21	21	22	19	21	17
ctrl5	16	17	15	18	18	16
ctrl6	21	20	17	19	18	19
ctrl7	17	19	18	18	19	18
ctrl8	16	18	17	18	16	14
ctrl9	17	18	17	16	16	20
ctrl10	19	17	19	18	17	15
ctrl11	19	18	20	17	18	20
ctrl12	18	19	20	19	21	19
ctrl13	18	19	20	18	20	20
ctrl14	19	18	19	18	18	17
ctrl15	19	18	19	18	19	18
ctrl16	20	19	18	18	21	21
ctrl17	20	21	22	22	18	17
ctrl18	19	19	18	18	17	17
ctrl19	20	17	18	19	18	20
ctrl20	18	17	18	16	14	19

RE: Right eye.

TZERO IOP	1_O	T5 MONTHS IOP	4_O
T7 DAYS IOP	2_O	T10 MONTHS IOP	5_O
T1 MONTH IOP	3_O	T13 MONTHS IOP	6_O

LE	1_0	2_0	3_0	4_0	5_0	6_0
ctrl1	18	18	19	19	19	20
ctrl2	18	18	18	19	18	19
ctrl3	18	18	19	17	20	19
ctrl4	20	19	18	19	20	19
ctrl5	17	16	16	18	17	16
ctrl6	18	18	18	20	18	17
ctrl7	18	18	19	19	18	19
ctrl8	17	19	18	17	19	15
ctrl9	19	19	18	17	16	20
ctrl10	17	17	17	18	18	15
ctrl11	18	19	20	19	17	19
ctrl12	18	18	19	18	20	20
ctrl13	18	18	19	18	19	21
ctrl14	18	20	17	20	17	18
ctrl15	20	18	19	18	19	19
ctrl16	19	18	19	19	19	19
ctrl17	21	20	18	19	18	18
ctrl18	18	19	19	17	18	16
ctrl19	19	19	18	19	19	20
ctrl20	19	18	20	18	20	19

LE: Left eye.

TZERO IOP BEFORE OMT	1_O	T5 MONTHS IOP BEFORE OMT	4_O
T7 DAYS IOP BEFORE OMT	2_O	T10 MONTHS IOP BEFORE OMT	5_O
T1 MONTH IOP BEFORE OMT	3_O	T13 MONTHS IOP BEFORE OMT	6_O

The fluctuations in pressure in the control group maintained a random evolution while still remaining within the normal range.

The visual field tests, carried out over 14 months showed up neither significant differences between the two groups nor significant differences in the AD.

Discussion

The inspiration for this pilot study of integrated medicine arose from the growing interest primarily on the part of neurobiologists and secondarily ophthalmologists, on the circulation of the CSF in connection with eye fluids. Recent studies have shown how the CSF enters the optic nerve of rodents by way of the Glymphatic System, and suggest that further research on humans could take us to the same conclusions [4, 5].

Wostyn, Killer and De Deyn explain how the stasis of the glymphatic system, in the region of the lamina cribrosa of the optic nerve, could influence the structure of the axons of the ganglion cells developing glaucoma [45].

According to these new models, the CSF is secreted not only from the choroid plexus located inside the cerebral ventricles, but also inside the arterial paravascular spaces made up of glia cells, called Virchow and Robin Spaces (VRS) [46]. VRS's are made up of astrocyte pedicels which are wrapped around the capillaries of the cerebral parenchyma, and these astrocyte sheaths present numerous acquaporine-4 canals, thus facilitating the passage of the CSF into the interstices and its intermixing with the interstitial fluid (IF) [46–48].

CSF and IF seem to mingle in the interstitial spaces, and which then drain off interstitial solutes and catabolytes, through lymphatic ducts present in the dura mater located in correspondence with cranial sinuses. This system of ducts flows together in the cervical lymph ducts, and exits through the right lymph duct and the thoracic duct into the subclavian veins [1–3, 47, 48]. The fluids inside this system of perivascular canals are driven by arterial pulsation and diaphragmatic breathing [39–41, 48, 49].

Various studies carried out in vivo on rodents and recently also on humans show how the function of catabolyte clearance attributed to the glymphatic system takes place mainly during deep sleep and is almost absent during waking hours [2, 50–53]. This function takes place via an expansion of the interstitial space, facilitating the ingress of CSF to the brain and its interchange with the IF. An eventual malfunction of the glymphatic system and the consequent deficit in the elimination of catabolytes, can therefore influence the homeostasis of the CNS, favouring the development of central neurodegenerative disease due to a build-up of neurotoxins [54–58].

In a 2006 article, Flammer and Pache attempted to bring glaucoma into a wider medical discussion, and debated the systemic peculiarities revealed in POAG. These systemic alterations include: cardiovascular system, autonomous nervous system, immune system, as well as endocrinological, psychological and sleep disturbances [59].

Every patient at every osteopathy session was treated according to whatever clinical evidence was discovered during the osteopathic evaluation test, and ascertained from their relative medical histories.

This "blackbox" practice can be described as an individually tailored treatment for every patient and is performed in accordance with the problems and medical conditions of each individual [37, 60].

The results are arrived at through an analysis of the results of the initial tests and a comparison with the final tests.

In the TG, the osteopathic tests showed up frequent SD of the diaphragm and those organs below the diaphragm, the ribcage, the occipital area and of the cervical tract C1-C2. At the end of the session exercises were recommended [60], to encourage correct diaphragmatic breathing, especially in sedentary patients who were found to have restricted ribcage mobility often associated with shallow and irregular breathing.

Current knowledge in the medical field identifies the thoracic diaphragm as a principle factor for the lymphatic and CSF circulation [39–41]. A diaphragm is a transverse membrane which creates two distinct zones, whose correct functioning depends upon the maintenance and balancing of the pressures within the two zones it divides.

Osteopathy recognizes other structures as diaphragms including the pelvic floor, the thoracic outlet, the buccal floor, the diaphragm of the hypophysis and the tentorium cerebelli. These structures are considered to be general purpose pumps which permit the expansion, the distribution, the transmission and the regulation of the fluids (blood, CSF and lymph) to the peripheries [37, 60].

Recently, osteopathic medicine has proposed manipulations which seem to influence the flow of CSF, for conditions such as chronic fatigue syndrome [61], where this flow appears to be reduced. OMth also appears to induce changes during sleep in healthy patients [62]. By virtue of these considerations, the improvement or the resolution of visceral or structural problems could be extended throughout the body beyond the cranial and cervical regions, to include functional areas of the lymphatic system [37, 60].

Support for the efficiency of osteopathic treatments in neurodegenerative pathologies such as glaucoma, could be attributed to the positive influence that these treatments would have not only on the IOP but also on cerebral vascular perfusion, being then also capable of influencing venous, lymphatic and CSF circulation by facilitating its drainage [20–35].

As regards future projects, we have planned a follow-up of at least 3 years and the use of Angio-OCT for measuring eventual variations in the vascularization of the retina and of the optic nerve subsequent to OMth.

Conclusions

A reduction in pressure already detected after the first treatment, which was persistent and statistically significant at every manipulation session carried out, shows that in some selected cases it is possible to influence ocular pressure by means of osteopathic treatments, without interfering with in-place pharmacological regimes.

Therefore, this places before the panorama of scientific research a possible starting point for future research and investigation into POAG in both the ophthalmological and osteopathic spheres. However, the small sample and an insufficiently long follow-up do not permit us to evaluate the eventual progression and the stabilization of the disease (visual field), and cannot provide conclusive answers on the duration of the pressure-reducing effects of OMth.

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